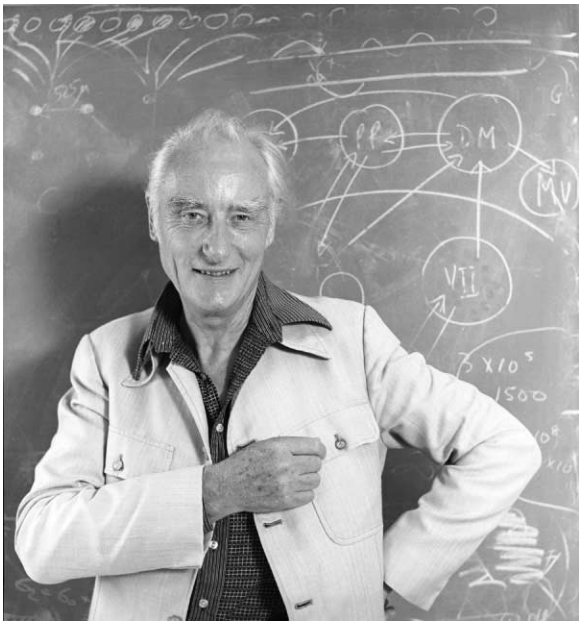
Cell, Vol. 119, 1–2, October 1, 2004, Copyright ©2004 by Cell Press

Obituary

Francis Crick (1916–2004)



Francis Crick

It has often been asserted that the discovery of the structure of DNA in 1953 was the starting point for molecular biology. Whether or not this is true, it cannot be doubted that Francis Crick became a dominant figure in the early years of molecular biology. In those years there was a continual interaction between theory and experiment, in which Crick paid a leading role. I was in Cambridge at the time and on several occasions enjoyed the lucidity and clear thinking of his seminars, as well as his entertaining style. He was able to define an important problem and then indicate what the solution might be. Nothing better illustrates his remarkable abilities than a lecture on protein synthesis he delivered in 1957 to a Symposium organized by the Society for Experimental Biology, which I was privileged to attend. For the first time, he made it clear that there were only 20 primary amino acids in protein, so the coding problem became the mechanism by which the linear sequence of four DNA bases specified the sequence of 20 amino acids in proteins. He also suggested that there would have to be a series of intermediate adaptor molecules specific for each amino acid—a remarkable prediction of the existence of tRNA molecules with their three-base anticodons. In addition, he expounded what he called the "central dogma" of molecular biology, namely, that information (by which he meant sequence information) could be transferred from nucleic acid to protein or from nucleic acid to nucleic acid, but not from protein to nucleic acid or protein to protein. The central dogma was in fact a working hypothesis that has stood the test of time remarkably well, and those who thought that the discovery of reverse transcriptase contravened the dogma were mistaken.

Crick was very approachable and helpful to younger scientists. I went to see him in 1958 to ask whether mismatched bases formed during genetic recombination would be chemically unstable. The answer was no, but with typical prescience, he added "but you could propose that there are enzymes able to recognize and repair such mismatches." At the time, the study of DNA repair was in its infancy. During the course of our discussion, Crick excitedly told me about the new, as yet unpublished results of Meselson and Stahl. They provided direct evidence for the "semi-conservative" replication of DNA, as predicted by the Watson-Crick structure. I was surprised by his excitement because as a naive graduate student, I simply assumed that DNA must replicate in this manner. In l961, a seminar by Crick was announced on acridine-induced mutagenesis in bacteriophage T4. It did not sound too exciting but turned out to be a revelation because it provided a proof that the DNA code was read in triplets. William Hayes, one of the founders of bacterial genetics, referred to the results, which were soon published in *Nature*, as "this brilliantly imaginative study by Crick, Barnett, Brenner and Watts-Tobin which ranks as a masterpiece of genetic analysis." In his book *What Mad Pursuit*, Crick recalls how he and Leslie Barnett first discovered that three closely linked addition (or deletion) mutations had a wild-type phenotype: "I looked across at Leslie. 'Do you realise,' I said, 'that you and I are the only people in the world who know it's a triplet code?'" When Crick first proposed that these experiments should be done, his colleagues thought that the predictions were far too outlandish to be taken seriously, and that is why he began to do the experiments himself. I attended another brilliant lecture by Crick soon after the triplet code was deciphered. By analyzing mutations producing single amino acid substitutions in proteins in prokaryotes and eukaryotes, he deduced that the code must be universal in all organisms. (Mutations moved the coding triplet vertically or horizontally in the coding box, but never diagonally, which requires at least two base changes.) After bacteriophage, Crick and Sydney Brenner turned their attention to the nematode *Caenorhabditis elegans* and wrote a proposal to use it for the study of development and the nervous system. The success of innumerable subsequent projects with this tiny animal eventually earned Brenner the Nobel Prize, which Crick himself had been awarded forty years earlier.

Crick had a long-standing interest in the study of the nervous system and the brain. Indeed, when he decided to move from physics to biology, after his work on mines during the war at the Admiralty, he had to make the decision between research on vision or on the borderline between the living and the nonliving. "The decision was a hard one," he wrote. After a two year spell at the

Strangeways Laboratory, Cambridge, he was fortunate to be accepted in the late 1940s as a 33-year-old graduate student at the Cavendish Laboratory, where Max Perutz and John Kendrew were studying hemoglobin and myoglobin by X-ray diffraction under the directorship of Lawrance Bragg. Crick could not have found a better environment because his background in physics and his new interests in biology complemented each other, and he was also able to make important theoretical contributions to the theory of X-ray diffraction. It was also fortunate that James Watson arrived at the laboratory in 1951 because that led to the synergistic interaction that culminated—as all the world knows—in the discovery of the structure of DNA. There was one relative failure, and that was in the search for single amino acid substitutions in a protein resulting from mutation. The first studies were with lysozyme, but no differences were detected in the enzyme from different sources. However, Vernon Ingram was soon able to show that in sickle cell anemia there was a single amino acid change from the normal molecules. It was the first documented case, to be followed by a flood of further examples in other proteins.

In his book *Molecules and Men* (1966), Crick foresaw the extreme importance of understanding the human brain:

> Now there are some questions that affect us far more personally than others, and among these the working of the brain ranks high. It can be confidently stated that our present knowledge of the brain is so primitive—approximately at the stage of the four humours in medicine or of bleeding in therapy (what is psychoanalysis but mental bleeding?)—that when we have fuller knowledge our whole picture of ourselves is bound to change radically. Much that is now culturally acceptable will then seem to be nonsense. People with training in the arts still feel that in spite of the alterations made in their lives by technology—by the internal combustion engine, by penicillin, by the Bomb—modern science has little to do with what concerns them most deeply. As far as today's science is concerned that is partly true, but tomorrow's science is going to knock their culture right out from under them.

The book was based on three lectures at the University of Washington, Seattle, during which he demolished vitalism, and he included a memorable comment about natural selection: "A really beautiful mechanism, the discovery of which is one of the great intellectual triumphs of our civilisation." He also wrote: "The ultimate aim of the modern movement in biology is in fact to explain all biology in terms of physics and chemistry." That was his credo. Crick was an intellectual rationalist, and athiest. He resigned his fellowship at the new Churchill College, Cambridge when it was decided to build a chapel. He refused many honors but did accept the Order of Merit, which is conferred on the elite in the fields of literature, arts, and science.

When he moved from Cambridge to the Salk Institute, California, in 1977, he decided to take up the serious study of the brain. He was diligent in familiarizing himself with everything that was known. It was said that he sometimes exhausted visiting neurobiologists or psychologists with long discussions that probed their knowledge and expertise. During this period, through my friendship with Leslie Orgel, I saw Crick on several occasions, and on one occasion discussed the possibility that long-term memory might be based in the epigenetic methylation of DNA in neurons. The human brain is the most complicated biological object on this planet and is therefore the ultimate challenge to scientists. Crick was well aware of this and realized that only a step-by-step approach could ever be successful. He wrote a book *The Astonishing Hypothesis* (1994), explaining at the outset that "The Astonishing Hypothesis is that 'You,' your joys and your sorrows, your sense of personal identity and free will, are no more than the behaviour of a vast assemby of nerve cells and their associated molecules. As Lewis Carroll's Alice might have phrased it: 'You're nothing but a pack of neurons.' This hypothesis is so alien to most people who are alive today that it can truly be called astonishing." This short quotation strongly illustrates the character of the man. In a Millennium Issue of the Philosophical Transactions published in 2000 by the Royal Society, he emphasized the importance of molecular biology and the human genome sequence in future studies of neurobiology. He urged neuroscientists to pay more attention to new techniques of molecular biology, which could help advance their field of research. A final quotation from the end of this paper provides more character and flavor: "The point I want to stress is that neuroscientists should scan molecular biology for appropriate techniques but, most important, they should ask their molecular biology friends for new tools. They should tell them what their difficulties are and what they want to do. Once the word gets around that a certain type of problem exists it is surprising how often someone has a bright idea of how to solve it. So, don't be shy—ask! After all, exactly how our brains work is of vital interest to us all, so why shilly-shally."

It has been said of Crick that " he was effortlessly right all the time." In my view, he was the greatest scientist of the second half of the twentieth century, and his reputation can only grow in this one. Modern molecular biology is now awash with new information, and more and more is accumulating all the time. There is a huge need for scientists who have the particular qualities Crick so clearly displayed because it has become essential to see connections between disparate observations and to formulate new theoretical frameworks that can be rigorously tested by decisive experiments. It should be much more widely understood that to think and to talk incisively about a problem, as Crick frequently did, is as important as collecting new information. Let us hope that amongst the vast army of contemporary molecular biologists, there are a few, or even one, with the vision, the creativity, and the abilities of a Francis Crick.

Robin Holliday
12 Roma Court
West Pennant Hills
Sydney, NSW 2125
Australia

Correspondence: randl.holliday@bigpond.com